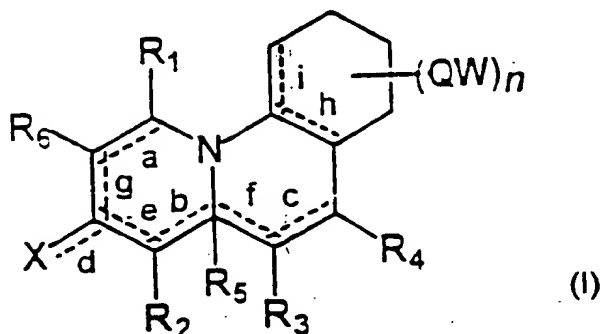


Claims

1. Fully and partially reduced benzo[c]-quinolizine compounds of formula (I)



wherein:

R₁, R₂, R₃, R₄, R₅, R₆, same or different, are chosen in the group consisting of: H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, norbornane, canphane, adamantane, phenyl, biphenyl, naphthyl, saturated or aromatic heterocycle containing one or more N atoms, halogen, CN, azide, NRR', C₁₋₈alkylamino, arylamino, C₁₋₈alkyloxy, aryloxy, COOR, CONRR', C(=O)R, wherein R and R', same or different, are chosen in the group consisting of: H, C₁₋₈alkyl, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, norbornane, canphane, adamantane, phenyl, biphenyl, naphthyl, ^{or} saturated or aromatic heterocycle containing one or more N atoms, phenyl-, biphenyl-, naphthyl-C₁₋₈alkyl;

R₅ is chosen in the group consisting of: H, C₁₋₈alkyl, C₁₋₈alkyl-phenyl, -biphenyl, -naphthyl, COOR, CN, , phenyl, biphenyl, naphthyl, saturated or aromatic heterocycle containing one or more N atoms, C₁₋₈alkyl-saturated or aromatic heterocycle containing one or more N atoms; C₁₋₈alkyl-saturated or aromatic heterocycle containing one or more N atoms -ribose-phosphate

X is chosen in the group consisting of: O, C(=O)R, COOR, NO₂, CONR'R wherein R and R' are as above defined;

Q is chosen in the group consisting of: simple bond, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, norbornane, canphane, adamantane, CO, CONR, NR, wherein R is as above defined;

W is chosen in the group consisting of: H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane,

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cyclooctane, norbornane, canphane, adamantane, trifluoromethyl, C₁₋₈alkoxy, C₁₋₈ alkoxy-C₁₋₈alkyl, phenyl-, biphenyl-, naphtyl-C₁₋₈alkyl, phenyl, biphenyl, naphtyl, phenyloxy, biphenyloxy, naphtyloxy, phenylamino, biphenylamino, naphtylamino, C₁₋₈alkylcarbonyl, phenylcarbonyl, biphenylcarbonyl, naphtylcarbonyl, phenylcarboxyl, biphenylcarboxyl, naphtylcarboxyl, phenylcarboxamide, biphenylcarboxamide, naphtylcarboxamide, halogen, CN, NRR', C₁₋₈alkylamino, saturated or aromatic heterocycle containing one or more N atoms wherein the groups alkyl, alkenyl, alkynyl, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, norbornane, canphane, adamantane, phenyl, biphenyl, naphtyl, saturated or aromatic heterocycle containing one or more N atoms, can be substituted; n is an integer comprised between 1 and 4; the symbol — means that the corresponding bonds a, b, c, d e, f, g, h and i can be a simple or a double bond; with the proviso that when b or f are a double bond then the group R₅ is absent;

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their pharmaceutically acceptable salts and esters.

2. Benzo[c]-quinolizine compounds of formula (I) according to Claim 1, wherein

$R_5 = H, C_{1-8}$ alkyl-phenyl, -biphenyl, -naphtyl, COOR, CN, phenyl, biphenyl, naphtyl, saturated or aromatic heterocycle containing one or more N atoms, C_{1-8}

C_{1-8} alkyl-saturated or aromatic heterocycle containing one or more N atoms; or a

group C_{1-8} alkyl-saturated or aromatic heterocycle containing one or more N atoms -ribose-phosphate

$X = O, COOH$

$Q =$ simple bond, CO, CONR, NR (wherein R is as above defined) $W = H, F, Cl,$

Br, Me, t-butyl, C_{1-8} alkoxy, 2,5-dimethylhexyl, trifluoromethyl, 2,5-(di-trifluoromethyl)-phenyl, 4-methoxy-phenyl, 4-fluoro-phenyl, phenyl, phenyl- C_{1-8} alkyl, C_{1-8} alkylcarbonyl, phenylcarbonyl.

$n = 1$ and 2

$R_1, R_2, R_3, R_4, R_5 = H, Me, CN, phenyl, COOR, CONRR'$ (wherein R and R' are as above defined).

3. Benzo[c]-quinolizine compounds according to Claim 1 of formula :

2,3,4,4a,5,6,6a,7,8,9,10,10a-dodecahydro-(1H)-benzo[c]quinolizin-3-one;

8-chloro-2,3,4,4a,5,6,6a,7,8,9,10,10a-dodecahydro-(1H)-benzo[c]quinolizin-3-one;

2,3,4,4a,5,6,6a,7,8,9,10,10a-dodecahydro-8-methyl-(1H)-benzo[c]quinolizin-3-one;

2,3,4,4a,5,6,6a,7,8,9,10,10a-dodecahydro-4-methyl-(1H)-benzo[c]quinolizin-3-one;

2,3,4,4a,5,6,6a,7,8,9,10,10a-dodecahydro-1-methyl-(1H)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-(1H)-benzo[c]quinolizin-3-one;

8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-(1H)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-8-methyl-(1H)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-4-methyl-(1H)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-1-methyl-(1H)-benzo[c]quinolizin-3-one;

(4a α , 6a β , 10a α)-3,4,5,6,6a,7,8,9,10,10a-decahydro-(4aH)benzo[c]quinolizin-3-one;

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(4a β , 6a β , 10a α)-3,4,5,6,6a,7,8,9,10,10a-decahydro-(4aH)benzo[c]quinoliz-3-one;

3,4,5,6,6a,7,8,9,10,10a-decahydro-(4aH)-benzo[c]quinolizin-3-one;

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8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-8-methyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-4-methyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-1-methyl-(4a*H*)-benzo[c]quinolizin-3-one;
8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-4-methyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-4,8-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-1-methyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-1,4-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-4-methyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-4,8-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;
8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-1-methyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-1,8-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-5-methyl-(1*H*)-benzo[c]quinolizin-3-one;
8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-5-methyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-5,8-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-4,5-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-1,5-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-5-methyl-(4a*H*)-benzo[c]quinolizin-3-one;
8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-5-methyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-5,8-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-4,5-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

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3,4,5,6,6a,7,8,9,10,10a-decahydro-1,5-dimethyl-(4aH)-benzo[c]quinolizin-3-one;

8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-4,5-dimethyl-(1H)-benzo[c]quinolizin-3-one;

5 2,3,5,6,6a,7,8,9,10,10a-decahydro-4,5,8-trimethyl-(1H)-benzo[c]quinolizin-3-one;

8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-1,5-dimethyl-(1H)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-1,4,5-trimethyl-(1H)-benzo[c]quinolizin-3-one;

10 8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-4,5-dimethyl-(4aH)-benzo[c]quinolizin-3-one;

3,4,5,6,6a,7,8,9,10,10a-decahydro-4,5,8-trimethyl-(4aH)-benzo[c]quinolizin-3-one;

8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-1,5-dimethyl-(4aH)-benzo[c]quinolizin-3-one;

3,4,5,6,6a,7,8,9,10,10a-decahydro-1,5,8-trimethyl-(4aH)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-6-methyl-(1H)-benzo[c]quinolizin-3-one;

20 8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-6-methyl-(1H)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-6,8-dimethyl-(1H)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-4,6-dimethyl-(1H)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-1,6-dimethyl-(1H)-benzo[c]quinolizin-3-one;

25 3,4,5,6,6a,7,8,9,10,10a-decahydro-6-methyl-(4aH)-benzo[c]quinolizin-3-one;

8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-6-methyl-(4aH)-benzo[c]quinolizin-3-one;

3,4,5,6,6a,7,8,9,10,10a-decahydro-6,8-dimethyl-(4aH)-benzo[c]quinolizin-3-one;

30 3,4,5,6,6a,7,8,9,10,10a-decahydro-4,6-dimethyl-(4aH)-benzo[c]quinolizin-3-one;

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3,4,5,6,6a,7,8,9,10,10a-decahydro-1,6-dimethyl-(4aH)-benzo[c]quinolizin-3-one;

8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-4,6-dimethyl-(1H)-benzo[c]quinolizin-3-one;

5 2,3,5,6,6a,7,8,9,10,10a-decahydro-4,6,8-trimethyl-(1H)-benzo[c]quinolizin-3-one;

8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-1,6-dimethyl-(1H)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-1,4,6-trimethyl-(1H)-benzo[c]quinolizin-3-one;

10 8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-4,6-dimethyl-(4aH)-benzo[c]quinolizin-3-one;

3,4,5,6,6a,7,8,9,10,10a-decahydro-4,6,8-trimethyl-(4aH)-benzo[c]quinolizin-3-one;

15 8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-1,6-dimethyl-(4aH)-benzo[c]quinolizin-3-one;

3,4,5,6,6a,7,8,9,10,10a-decahydro-1,6,8-trimethyl-(4aH)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-5,6-dimethyl-(1H)-benzo[c]quinolizin-3-one;

20 8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-5,6-dimethyl-(1H)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-5,6,8-trimethyl-(1H)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-4,5,6-trimethyl-(1H)-benzo[c]quinolizin-3-one;

25 2,3,5,6,6a,7,8,9,10,10a-decahydro-1,5,6-trimethyl-(1H)-benzo[c]quinolizin-3-one;

3,4,5,6,6a,7,8,9,10,10a-decahydro-5,6-dimethyl-(4aH)-benzo[c]quinolizin-3-one;

30 8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-5,6-dimethyl-(4aH)-benzo[c]quinolizin-3-one;

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3,4,5,6,6a,7,8,9,10,10a-decahydro-4,5,6-trimethyl-(4a*H*)-benzo[*c*]quinolizin-3-one;

8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-4,5,6-trimethyl-(1*H*)-benzo[*c*]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-4,5,6,8-tetramethyl-(1*H*)-benzo[*c*]quinolizin-3-one:

8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-1,5,6-trimethyl-(1*H*)-benzo[*c*]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-1,4,5,6-tetramethyl-(1*H*)-benzo[*c*]quinolizin-3-one;

8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-4,5,6-trimethyl-(4a*H*)-benzo[*c*]quinolizin-3-one;

3,4,5,6,6a,7,8,9,10,10a-decahydro-4,5,6,8-tetramethyl-(4aH)-benzo[c]quinolizin-3-one;

8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-1,5,6-trimethyl-(4a*H*)-benzo[*c*]quinolizin-3-one;

3,4,5,6,6a,7,8,9,10,10a-decahydro-1,5,6,8-tetramethyl-(4a*H*)-benzo[*c*]quinolizin-3-one;

5,6,6a,7,8,9,10,10a-octahydro-(3*H*)-benzo[*c*]quinolizin-3-one;

8-chloro-5,6,6a,7,8,9,10,10a-octahydro-(3*H*)-benzo[*c*]quinolizin-3-one;

25 5,6,6a,7,8,9,10,10a-octahydro-8-methyl-(3*H*)-benzo[*c*]quinolizin-3-one;

5.6.6a.7.8.9.10.10a-octahydro-4-methyl-(3*H*)-benzo[*c*]quinolizin-3-one;

8-chloro-5,6,6a,7,8,9,10,10a-octahydro-4-methyl-(3*H*)-benzo[*c*]quinolizin-3-one;

5,6,6a,7,8,9,10,10a-octahydro-4,8-dimethyl-(3*H*)-benzo[*c*]quinolizin-3-one;

2,3,5,6,7,8,9,10-octahydro-(1*H*)-benzo[*c*]quinolizin-3-one;

30 8-chloro-2,3,5,6,7,8,9,10-octahydro-(1*H*)-benzo[*c*]quinolizin-3-one;

2,3,5,6,7,8,9,10-octahydro-8-methyl-(1*H*)-benzo[*c*]quinolizin-3-one;

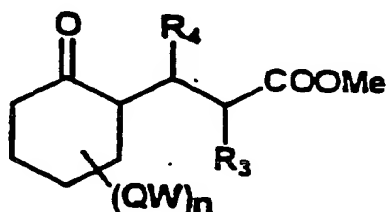
2,3,5,6,6a,7,8,9-octahydro-(1*H*)-benzo[*c*]quinolizin-3-one;

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8-chloro-2,3,5,6,6a,7,8,9-octahydro-(1*H*)-benzo[c]quinolizin-3-one;
 2,3,5,6,6a,7,8,9-octahydro-8-methyl-(1*H*)-benzo[c]quinolizin-3-one;
 4a-benzyl-3,4,5,6,6a,7,8,9,10,10a-decahydro-(4a*H*)-benzo[c]quinolizin-3-one;
 4a-benzyl-8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-(4a*H*)-
 5 benzo[c]quinolizin-3-one;
 4a-benzyl-3,4,5,6,6a,7,8,9,10,10a-decahydro-8-methyl-(4a*H*)-
 benzo[c]quinolizin-3-one;
 4a-benzyl-3,4,5,6,6a,7,8,9,10,10a-decahydro-4-methyl-(4a*H*)-
 benzo[c]quinolizin-3-one;
 4a-benzyl-3,4,5,6,6a,7,8,9,10,10a-decahydro-1-methyl-(4a*H*)-
 benzo[c]quinolizin-3-one;
 3,4,5,6,6a,7,8,9,10,10a-decahydro-4a-(4-pyridyl)methyl-(4a*H*)-
 benzo[c]quinolizin-3-one;
 8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-4a-(4-pyridyl)methyl-(4a*H*)-
 15 benzo[c]quinolizin-3-one;
 3,4,5,6,6a,7,8,9,10,10a-decahydro-8-methyl-4a-(4-pyridyl)methyl-(4a*H*)-
 benzo[c]quinolizin-3-one;
 3,4,5,6,6a,7,8,9,10,10a-decahydro-4-methyl-4a-(4-pyridyl)methyl-(4a*H*)-
 benzo[c]quinolizin-3-one;
 20 3,4,5,6,6a,7,8,9,10,10a-decahydro-1-methyl-4a-(4-pyridyl)methyl-(4a*H*)-
 benzo[c]quinolizin-3-one;

4. Process for the preparation of compounds according to any of claims 1-3 wherein:

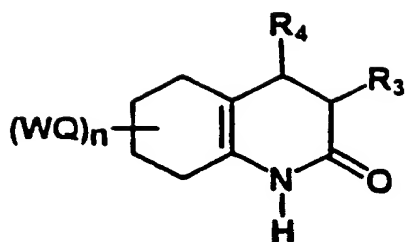
the ester-group of a compound of formula (2)



(2)

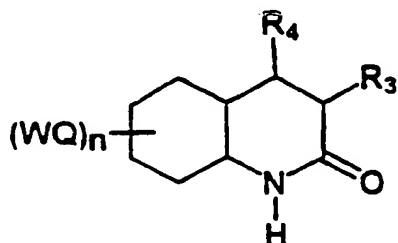
30 (wherein R_3 , R_4 and $(WQ)_n$ as defined in Claim 1)
 is cyclized to enamide (3)

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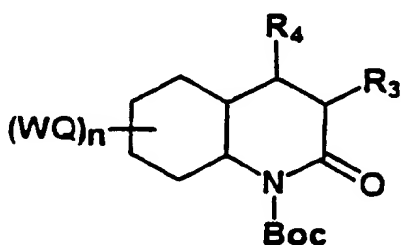
(3)

(wherein R_3 , R_4 and $(WQ)_n$ are as defined in Claim 1)
which is reduced to the amide (4)



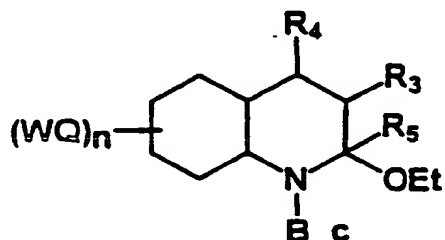
(4)

(wherein R_3 , R_4 and $(WQ)_n$ are as defined in Claim 1)
which is protected with a protecting group Boc to give the compound (5)



(5)

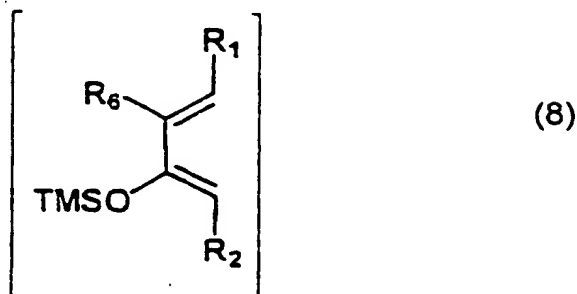
(wherein R_3 , R_4 and $(WQ)_n$ are as defined in Claim 1)
which is reduced to compound (6)



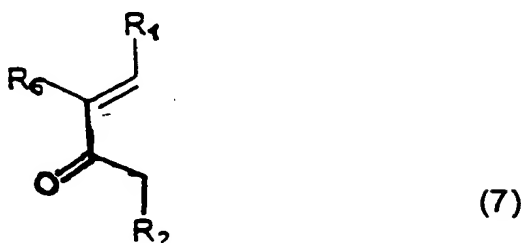
(6)

30

(wherein R_3 , R_4 , R_5 and $(WQ)_n$ are as defined in Claim 1)
and compound (6) is reacted with a silylether (8)



10 (wherein R_1 , R_2 and R_6 are as defined in Claim 1)
prepared "in situ" by reacting a vinyl-ketone (7)



20 (wherein R_1 , R_2 , R_6 are as above defined) with a silylating agent as
trimethylsilyltrifluorometansulphonic anhydride (TMSOTf) and are finally
hydrolized, for example with sodium hydrogencarbonate, to give the final
compound of formula (I) wherein $X = O$.

25 5. Process according to claim 4 wherein the possible introduction of the double
bonds in position a or b is performed by reaction of dichlorodicianoquinone
(DDQ) with the corresponding silylenoethers or by oxidation with quicksilver
acetate of the saturated compound obtained as claimed above and the possible
transformation of the group X is performed via the corresponding enoltriflates
and following carbonylation in the presence of palladium diacetate,
triphenylphosphine and the suitable nucleophilic reagent.

30 6. Process according to Claim 4 wherein the reaction between the compound
(6) and the silylether (8) is performed in the presence of $TiCl_4$.

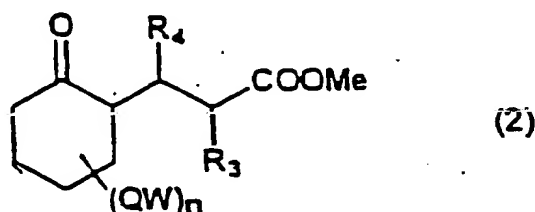
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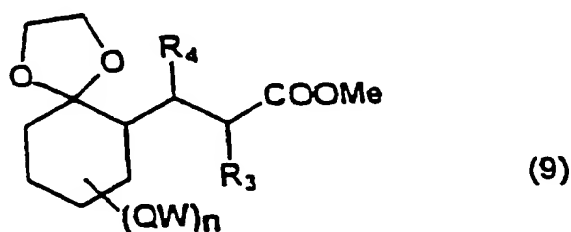
7. Process according to Claim 4 wherein the reaction between compound (6) and the silylether (8) is performed in the presence of TTMSOTf.

8. Process for the preparation of a compound of formula (I) according to any of claims 1-3, wherein:

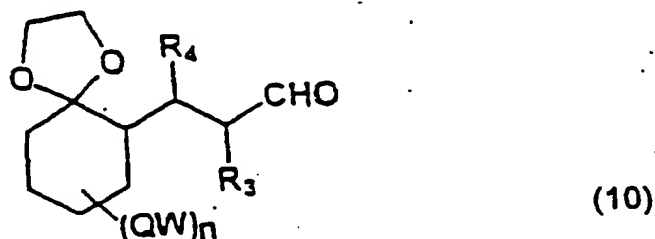
the carbonyl group of a compound of formula (2)



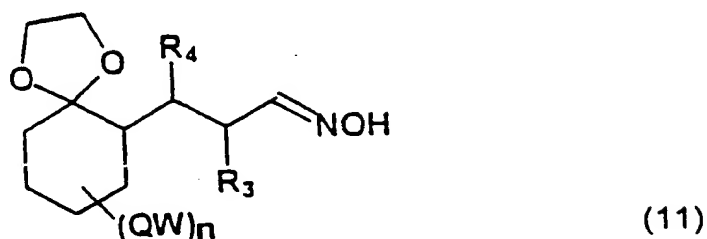
(wherein R_3 , R_4 , QW and n are as above defined) is protected as a ketal to give a compound (9)



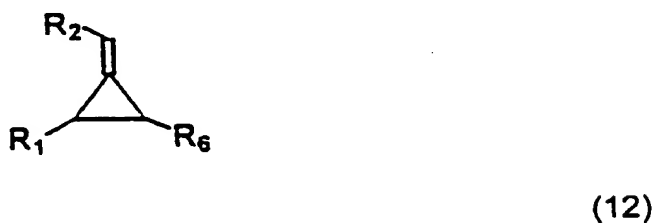
(wherein R_3 , R_4 , QW and n are as above defined) which is reduced to the corresponding aldehyde (10)



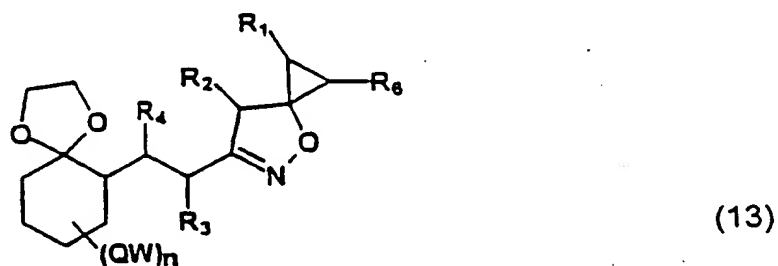
(wherein R_3 , R_4 , QW and n are as above defined) with DIBAL, and such
5 aldehyde is transformed into the oxime (11)



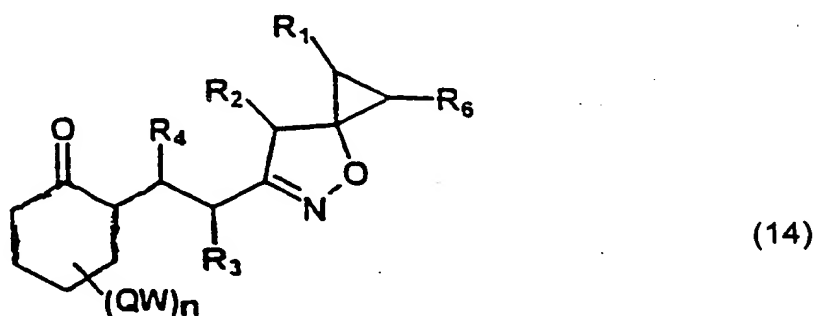
(wherein R_3 , R_4 , QW and n are as above defined) which is reacted with a
methylenecyclopropane derivative (12)



(wherein R_1 , R_2 and R_6 are as above defined) to give the isoxazoline (13)

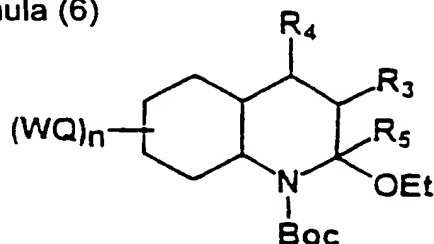


(wherein R_1 , R_2 , R_3 , R_4 , R_6 , QW and n are as above defined) which is
deprotected to the corresponding isoxazoline (14)



(wherein R_1 , R_2 , R_3 , R_4 , R_6 , QW and n are as above defined) which is rearranged to the final product of formula (I) wherein $X = O$, i or h is a double bond and the other substituents are as above defined.

9. Compound of formula (6)



(6)

wherein W, Q, n , R_3 , R_4 , R_5 are as defined in claim 1

10. Pharmaceutical composition wherein the active principle is a compound of formula (I) according to Claim 1 or mixtures thereof in combination with the suitable pharmaceutical acceptable excipients.

~~11. Pharmaceutical composition according to Claim 10 for use in the inhibition of the $5\alpha R$ -I and/or $5\alpha R$ -II iso-enzymes.~~

~~12. Pharmaceutical composition according to claims 10 and 11 in the form suitable for topic use.~~

13. Method for the treatment of pathologies related to 5α -reductase enzymes by administration to the patient of a pharmaceutically active amount of a pharmaceutical composition according to Claims 10.

14. Method according to claim 13 wherein the treated pathologies are acne, baldness, prostatic cancer and prostatic hypertrophy in men and hirsutism in women.

15. Use of compounds of formula (I) according to claim 1 as inhibitors of steroid 5α -reductase enzymes in plants.

16. Agricultural compositions for regulating the plant growth containing as active principle a compound of formula (I) according to Claim 1 or mixtures thereof possibly in combination with the additives commonly used in agriculture for this purposes.

17. Process for plant growth regulation wherein an effective quantity of a composition according to Claim 16 is distributed on the seeds and/or on the plants to treat.

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R27

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C1